The co-packaged product of pravastatin/aspirin was previously reviewed and was presented to the Cardio-Renal Advisory Committee on 18 January 2002. The advisory committee raised two objections to approval. The first was that not all doses were available in combination. In response to this objection, new formulations containing either 325 or 81 mg of aspirin will be available either with 20, 40 or 80 mg of pravastatin.

The second objection was a concern that aspirin as part of a co-packaged product, would inappropriately be continued or conversely, that the HMG CoA reductase inhibitor would be inappropriately discontinued at the time of a surgical procedure. This review consists of a summary and analysis of five publications that were submitted to the NDA on March 13, 2002. These publications are the sponsor's response to these concerns.

Publication #1

Heeschen C, Hamm CW, Laufs U, Snapinn S, Bohm M, White HD: Withdrawal of statins increases event rate in patients with acute coronary syndromes. Circulation; 2002; 105:1446-1452.

This was an observational study in a cohort of subjects who were enrolled in the PRISM study. These subjects had data available as to statin use at the time of entry and through the hospitalization. With respect to the PRISM study, a total of 3,232 subjects, who had evidence of unstable angina within 24 hours of study entry, received aspirin and were then randomized to additional therapy with tirofiban or heparin. The primary end point of the study was death, myocardial infarction or recurrent ischemia at each of the following time points 48-hours, 7-days and 30-days.

Of those enrolled into the PRISM study, 1,616 (50%) subjects had data available with respect to their statin use both pre-randomization as well as in-hospital. Of these subjects, 1,151 and 465 were not treated with or received statins at baseline, respectively. Of those treated with statins at baseline, 379 subjects continued statin use during hospitalization and 86 did not continue statin use. The comparison in this analysis is among those subjects whose statin usage was continued and those for whom it was discontinued.

The baseline characteristics, medical conditions and treatments did not differ in comparing those who continued and those who were discontinued from statins (data not shown here). The outcomes are shown in Table 1.

Table 1- Outcomes among those who had different statin status during the PRISM study

	No Statins N=1151	Statins continued N=369	Statins Discontinued N=86	P-value	Statins at baseline N=465*
48 Hours:					
Combined end point	68 (5.9%)	10 (2.6%)	9 (10.5%)	0.009	19 (4.1%)
Refractory ischemia	51 (4.4%)	12 (3.2%)	7 (8.1%)	0.032	19 (4.1%)
Death, MI	19 (1.7%)	2 (0.5%)	4 (4.7%)	0.21	6 (1.3%)
Death	3 (0.3%)	0	0	0.97	0
MI	16 (1.4%)	2 (0.5%)	4 (4.7%)	0.06	6 (1.3%)
Revascularization	6 (0.5%)	3 (0.8%)	1 (1.1%)	0.9	4 (0.9%)
7-Days:					
Combined end point	139 (12.1%)	36 (8.5%)	13 (15.1%)	0.25	49 (10.5%)
Refractory ischemia	122 (10.6%)	26 (6.9%)	12 (13.9%)	0.16	39 (8.2%)
Death, MI	61 (5.3%)	7 (1.9%)	8 (9.3%)	0.006	15 (3.2%)
Death	25 (2.2%)	2 (0.5%)	1 (1.2%)	0.58	3 (1%)
MI	36 (3.1%)	5 (1.6%)	7 (8.1%)	0.010	12 (2.6%)
Revascularization	235 (20.4%)	64 (17.3%)	22 (25.6%)	0.002	86 (18.5%)
30-Days:					
Combined end point	165 (14.3%)	38 (10.0%)	15 (17.4%)	0.07	53 (11.4%)
Refractory ischemia	125 (10.9%)	30 (7.9%)	13 (15.1%)	0.22	43 (9.2%)
Death, MI	86 (7.5%)	14 (3.7%)	12 (14.0%)	0.004	26 (5.6%)
Death	40 (3.5%)	6 (1.6%)	1 (1.2%)	0.31	7 (1.5%)
MI	46 (3.5%)	8 (2.1%)	11 (12.8%)	0.012	19 (4.1%)

p-values are derived from ANOVA.
*The statin at baseline group was added by this reviewer and was not included in the sponsor's calculations of p-Values.

The authors note that the outcomes among those that had their statins stopped were worse than among the subjects who had their statins continued during hospitalization. In particular, the combined end-point as well as death at 48-hours was worse than the cohort who discontinued statins when compared to the other cohorts.

(Comment: Considering those who were treated with statins at baseline (n=465), there did not appear to be a difference in outcome when compared to the no statin group (n=1151). Further subdividing the cohort into those in whom statin use was continued or discontinued must be viewed somewhat suspiciously. The cohort was not a randomized subgroup and the reason statins were discontinued is unclear. It is possible that those who were discontinued from statins were much sicker or rapidly deteriorated at baseline. They may have been made NPO because of their status during the first day of admission and therefore not given oral medication. In summary, this reviewer cannot differentiate whether the worst outcome was due to the cessation of therapy, or whether the cessation of statin therapy was due to the worsened status. In summary, this reviewer does not find this paper useful in deciding whether the short-term discontinuation of statin use is harmful).

Conclusion: This study result does not strongly support the contention that short term discontinuation of statin therapy has an acute effect on cardiovascular outcomes.

Publication # 2
Smith MS, Muir H, Hall R: Perioperative management of drug therapy, clinical considerations. Drugs; 1996; 51: (2) 238-259.

This publication reviews the available data on perioperative medication use. The publication does not supply any new data, but is a compendium of previous studies. These studies often rely on a surrogate marker or a very narrow population to ascertain whether the individual treatment should be discontinued or stopped at the time of a planned procedure. The treatments that were considered in the article were:

Antihypertensive medications (i.e. beta-adrenoreceptor blockers, alpha$_2$-adrenoreceptor agonists, calcium antagonists, ACE inhibitors) and antiarrhythmic agents.

CNS agents: including therapies for affective disorders (MAO inhibitors, tricyclic antidepressants and lithium); anti-psychotics, anxiolytics, anti-epileptics and drugs for the treatment of Parkinson's disease.

Drugs affecting the coagulation system: anticoagulants (e.g. heparin and warfarin), aspirin and non-steroidal anti-inflammatory drugs as well as thrombolytic agents

Glucocorticoids:

Aspirin:
The particular relevance of the publication is to the decision to continue aspirin during the perioperative period. The publication is a compendium of previously published studies, with no new investigations by the authors. The first issue broached in this section is the utility of a bleeding time test for defining the risk of hemorrhage during surgery. This issue is of minimal relevance to the issue at hand.

The largest source of data is the randomized data derived from the CLASP study (Collaborative Low-dose Aspirin Study in Pregnancy). The study was designed to determine if low dose aspirin (60 mg daily), relative to placebo alters the development of pre-eclampsia among pregnant women. (Note: this dose is lower than the proposed dose to be included in the combination product). The charts of 1,069 women who received epidural anesthesia were examined for evidence of adverse events (de Swiet M et al.; B. J Anaesth 1992: 69: 109). (note: the decision to perform the epidural anesthesia was not a randomized decision but a consequence of events that occurred to these subjects post randomization).

The review of the charts found 56 adverse events. Three of these events were possible epidural hemorrhages. Two of these events were in the placebo-treated subjects and one in the aspirin treated subjects. (Note: the severity of these events was not described. Since the event rate of the epidural hemorrhage is dependent on the skill of the anesthesiologist to perform the epidural anesthesia, the event rate on and off aspirin would not be expected to differ. The safety issue would be the severity of the bleed. This information was not available.).

The publication also referred to both a retrospective study among patients who received regional anesthesia for general surgery (Horlocker TT et al., -Anesth Analg 1990; 70: 631-4) and a prospective study in the same population (Horlocker TT et al.; Anesth Analg 1995, 80: 303-9). In the retrospective study, the outcome of 1,013 subjects who had a regional block prior to orthopedic surgery was collected for episodes of epidural hematoma. Of these patients, 39% were receiving preoperatively NSAID or aspirin. The review found no incidence of hematoma formation. In the prospective study by the same authors 924 subjects undergoing similar anesthesia for similar orthopedic procedures in which approximately 40% received NSAID or aspirin were examined for epidural hematoma. Again, the publication notes no increase in epidural hematoma rates.

Another study (Owens et al.; Anesth Analg 1986: 65:120-7) found among 33 cases of spinal hematoma one event that might have been related to post-operative use of aspirin.

For use prior to a procedure involving epidural blockade, the authors recommend albeit without data.

"Where it can be safely done without compromising patient's cardiac status, aspirin should be discontinued prior to surgery to prevent the increased risk of bleeding"

(Comment: The data base does not deal with the issues of bleeding form the infusion sites, the number of transfusions extra required or other hemorrhagic events, dehiscence of wound, stroke, gastrointestinal bleeds etc).

Conclusion: The strength of data for either stopping or continuing aspirin is not strongly supported by data as derived from this publication.

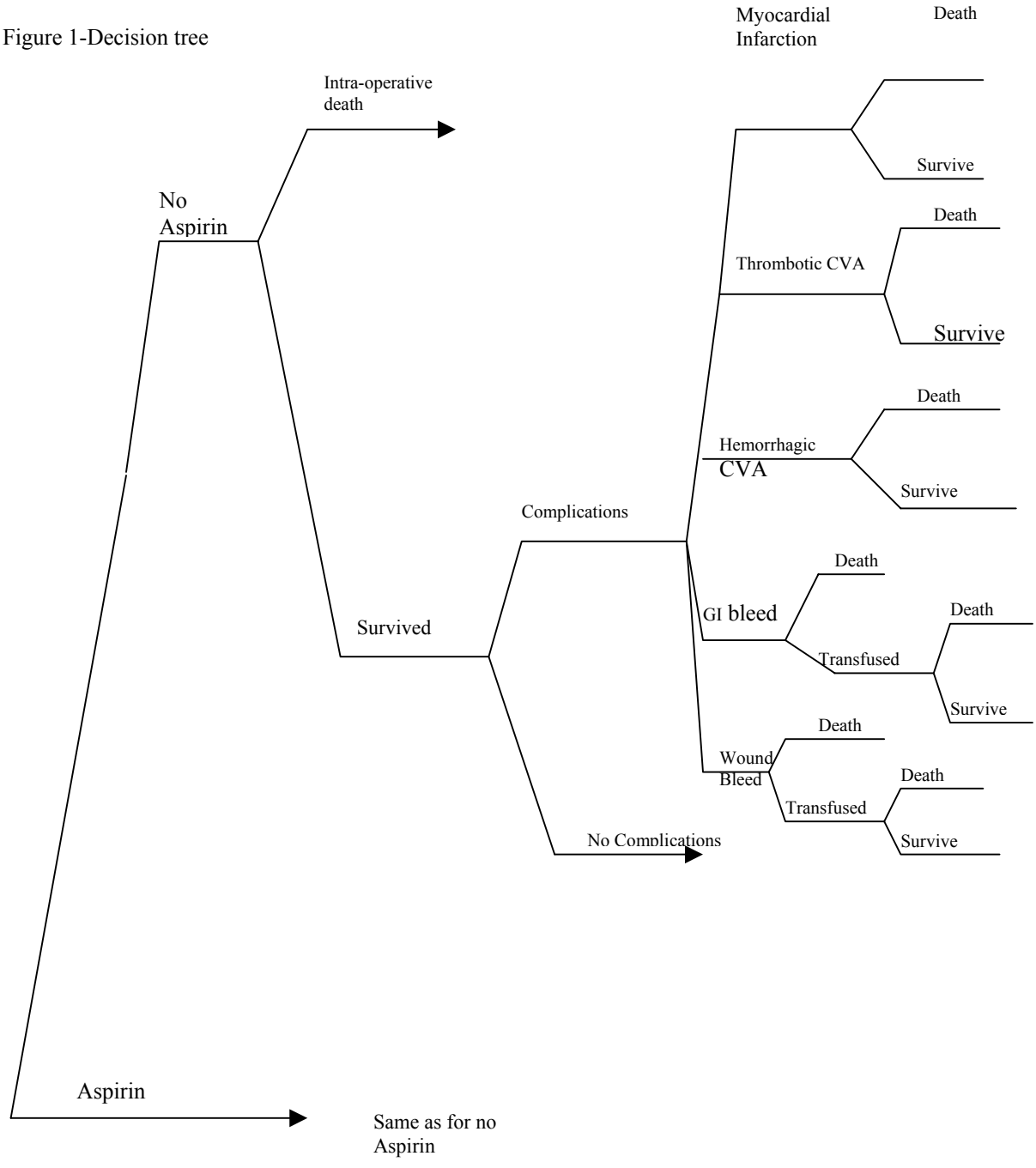
Publication # 3

Nelipovitz DT, Bryson GL, Nichol G: The effect of perioperative aspirin therapy in peripheral vascular surgery: A decision analysis. Anesth Analg; 2001; 93:573-80.

This publication, using a decision tree approach, explores the relative benefit of discontinuing or continuing aspirin treatment in a population undergoing an infra-inguinal revascularization procedure. There are no randomized clinical studies that specifically address the benefit/disadvantage to continue or discontinue aspirin therapy at the time of the revascularization procedure.

The decision tree analyzed by the authors is shown below.

Figure 1-Decision tree



Subjects could either receive aspirin or have aspirin discontinued at the time of surgery. Complications that are considered are myocardial infarction, thrombotic and hemorrhagic CVAs, and GI or incisional bleeds. The decision tree presumed that, for this analysis, aspirin's effect both positive and negative has completely dissipated. The frequency of these events and the resulting outcomes were derived from a series of publications culled from a MEDLINE search. The authors utilized two measures to quantify the results of a particular outcome. The first measure is the survival rates. The second is the utility value, the quantitative assessment of the subject's quality of life as a consequence of the event.

The specific values and the sources of the value are shown in Table 2. The author's included data from both randomized and cohort studies. Standardized life tables were used to assess survival after the perioperative period. Since there was no data in the literature, the authors assumed that the mortality risk from an incisional bleed was 5%. The results of the author's analysis are shown in Table 3.

Table 2. Studies, their size and the population enrolled with event rate and mortality rates as well as the relative effect of aspirin and the 95% CI

Event	Study	Type	N=	Population	Event Rate	Mortality
Myocardial Infarction	Christeropherson et al.;[1]	RCT	100	PVD surgery	4%	50%
	Stuhmeier et al.;[2]	RCT	297	Vascular Surgery	1.3 %	50%
	Bode et al.;[3]	RCT	425	PVD surgery	4.5 %	N/A
	Iloprost Bypass Group [4]	RCT	577	PVD surgery	4.1 %	N/A
	Sarac et al.; [5]	RCT	56	PVD surgery	5.4 %	N/A
	Ouyang et al.; [6]	Cohort	24	PVD surgery	8.3 %	N/A
	Mamode et al,; [7]	Cohort	191	PVD surgery	7.3 %	57%
	Von Knorring and Lepantalo [8]	Cohort	105	PVD surgery	2.9 %	66%
	Taylor et al.; [9]	Cohort	207	PVD surgery	3.4 %	29%
	Cutler et al.; [10]	Cohort	130	PVD surgery	5.4 %	71%
	Yeager et al.; [11]	Cohort	572	PVD surgery	3.5 %	25%
	Model Value (weighted mean)				**3.98 %**	**41.9%**
Thrombotic CVA	Hart and Hindman [12]	Cohort	125	PVD surgery	N/A	17.0 %
	Iloprost Bypass Group [4]	RCT	577	PVD surgery	0.97 %	N/A
	Barnes et al.; [13]	Cohort	125	PVD surgery	1.6 %	N/A
	Turnipseed et al.; [14]	Cohort	160	PVD surgery	3.1 %	N/A
	Kelley and Kovacs [15]	Cohort	171	CVA patients	N/A	20 %
	Model Value (weighted mean)				**1.46 %**	18.7%
Hemorrhagic CVA	Anderson et al.; [16]	Cohort	492	CVA Patients	N/A	46%
	Petty et al.; [17]	Cohort	339	CVA Patients	N/A	30%
	Model Value (weighted mean)				**0.3 %**	**35.4%**
GI bleed	Shina et al.; [18]	Retrospective	309	PVD surgery	0.3	N/A
	Peura et al.; [19]	Cohort	1235	GI bleeds	N/A	2.1%
	Model Value (weighted mean)				**0.3%**	**2.1%**
Incisional Bleed	Clyne et al.; [20]	RCT	70	PVD surgery	1.4 %	N/A
	Davies et al.;[21]	Cohort	138	PVD surgery	10.1 %	N/A
	McCollum et al.;[22]	RCT	263	PVD surgery	3.4 %	N/A
	Model Value (weighted mean)				**5.07%**	**N/A**
Relative Risk of Aspirin					RR ASA	CI
Myocardial Infarction	He et al.; [23]	Systematic Review	55462	AHD	0.68	0.62-0.74
	ATC [24]	Systematic Review	68698	AHD	0.68	N/A
	Model Value (weighted mean)				**0.68**	
Thrombotic CVA	He at al.; [23]	Systematic Review	55462	AHD	0.82	0.73-0.92
	ATC [24]	Systematic Review	65941	AHD	0.72	N/A
	Model Value (weighted mean)				**0.77**	
Hemorrhagic CVA	He et al.; [23]	Systematic Review	55462	AHD	1.84	1.24-2.74
	Model Value (weighted mean)				**1.84**	
GI Bleed	Peura et al.; [19]	Cohort	1235	GI Bleeds	2.76	2.03-3.74
	Kelly et al.; [25]	Case control	1752	GI bleeds	2.3	1.3-4.3
	Model Value (weighted mean)				**2.53**	
Incisional Bleed	ATC [24]	Systemic Review	3999	PVD surgery	1.52	N/A
	Model Value (weighted mean)				**1.52**	

RCT=Randomized clinical trial PVD=peripheral vascular disease CVA= cerebrovascular accident

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Table 3. Specific parameters used and outcomes.

Strategy	MI	Thrombotic CVA	Hemorrhagic CVA	Gastric Bleed	Incisional Bleed	All adverse events	Mortality	Crude life expectancy (yr)	Quality –adjusted life expectancy (QALYs)
- ASA	4.61 %	1.69%	0.37%	0.35 %	5.88 %	12.9 %	2.78 %	14.83	14.72
+ ASA	2.71%	1.12%	0.59 %	0.76 %	7.71 %	12.89 %	2.05 %	14.89	14.79

Based on this analysis, the authors anticipate a decrease in morality of 0.73%. (2.78%-3.05%) at the time of the procedure.

The authors also performed a sensitivity analysis of the data. One or more of parameters was altered to determine the effect on the analyzed outcome. Based on the sensitivity analysis,. the utility value of continuing aspirin exceeds the risk of bleeding from continued aspirin use as long as the risk of a myocardial infarction is approximately ¼ that of the risk of incissional bleed (all other parameters held constant).

(Comments: The authors who devised this decision-tree analysis were well aware of its short comings. Below are ome of the authors as well as some of the reviewer's assessment of the decision tree analysis.

- The values culled from the literature are frequently estimates derived from distantly related situations. For example, risk the reduction in myocardial infarction rate with aspirin is derived from a meta analysis of a predominantly secondary prevention population. It is unclear if the same risk reduction would occur in the perio-operative population. It is clear that some process during the perioperative period increases the frequency of myocardial infarctions and thrombotic and hemorrhagic strokes over the equivalent time from in a non-operative situation. It is, therefore, unclear if aspirin's benefits in platelet aggregation would be sufficient to mitigate the events occuring during the perio-operative period.

- The point estimates used (and the 95 % CI) are essentially meta-analyses. Each of these estimates are therefore, subject to the same limitations of any meta analyses. The uncertainty of any estimate for the overall effect is the composite of the uncertaity of each component that went into that estimate.

- Some of the estimates are derived from scant data, and with doses of aspirin that are unknown. The mid- point of the estimated effect is chosen by the authors, but may be highly inaccurate, particularly when there are few available studies which define that estimate.

- The number used in the calculations are close to but not equivalent to the numbers from the meat-analysis derived data. The values in Table 2 are weighted averages, the values used in constructing Table 3 are mean avearages (communication with the author).

- The author's presume that the risks of aspirin are limited to the frequency of events. The severity of the event is not presumed to be altered with aspirin).

In summary, the publication is of interest in its elegance. Its accuracy, however, is unknown. A proper randomized clinical study has not been performed. The relevance of the conclusion is in this reviewer's estimate, speculative.

Publication # 4

Spell NO: Stopping and restarting medications in the perioperative period. Medical Clinics of N Amer; 85; 5 1117-1128

This is a review article that discusses the need to discontinue certain treatments prior to surgery. With respect to aspirin, no additional studies or new information is supplied. Based on the concern for the possibility of serious sequelae during certain forms of surgery e.g., neurosurgical, opthalmological or vascular, cessation of aspirin therapy may be warranted. For cardiovascular surgeries a consensus is absent, "…although it is likely that aspirin increases perioperative mortality, evidence of significant effects on morbidity and mortality is lacking".

Conclusion: This publication adds no additional information with respect to the risk of continuing aspirin during the perioperative period.

Publication # 5

Koch KT, Piek JJ, de Winter RAJ, Mulder K, Schorborgh CE, Tijssen GP, Lie KT: Two hour ambulation after coronary angioplasty and stenting with 6F guiding catheters and low dose heparin; Heart; 1999: 81 53:56

The purpose of the study described by the paper is to determine whether early ambulation (2 hours) after elective coronary angioplasty was safe. The study consisted of a 621 consecutive subjects treated at the Academic Medical Centre Mebergdreef, Amsterdam, Netherlands with elective angioplasty. Each of the procedures was performed using a 6F guiding catheter by the femoral approach with a standard dose of 5000 IU of heparin. Those patients given other anticoagulation were excluded from analysis. All patients were given aspirin at a dose of 100 mg/day. Patients who were stented also received ticlopidine at 250 mg daily. Haemostasis was applied by manual compression followed by the application of a manual compression bandage, after removal of the catheter sheath. Of the 621 subjects 300 patients were eligible for 2-hour ambulation. Five patients had bleeding complications at or immediately after ambulation (1.7%). A total of 9 subjects (including, one subject who had bleeding complications at ambulation). This result suggests that after low dose short-term aspirin regimens, excessive bleeding from the catheterization insertion site was not excessive.

◄

Overall Analysis: The supplied publications are only marginally pertinent to the safety of the continued use of aspirin during the peri-operative period. A randomized, prospective study in discontinuing or continuing aspirin in a whole series of situations defining the benefit/risk relationship has not been performed. The decision tree analysis by Nelipovitz is elegant in thought but of unknown accuracy and unknown applicability to the vast majority of situations for which the decision to discontinue aspirin would be relevant. The other publications are compendiums of data with the individual studies not really "on point".